UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/790,273 | 03/01/2004 | John W. Hanrahan | MGU-0027 | 3977 |

7590 08/08/2006

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053

| EXAMINER | |
|---|---|
| STANDLEY, STEVEN H | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1649 | |

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/790,273 | HANRAHAN ET AL. | |
| | Examiner | Art Unit | |
| | Steven H. Standley | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *1-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date ~~8/05~~ 5/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election with traverse of Group III (claims 7-8) in the reply filed on 5/26/06 is acknowledged. The traversal is on the ground(s) that the inventions are not distinct and further that there is no search burden. Applicant sites MPEP § 803, highlighting the phrase "and are patentable over each other," as a requirement for being distinct. Further, applicant argues that the inventions relate to a single inventive concept and therefore would not be a search burden. This is not found persuasive because the inventions are distinct as set forth in the requirement for restriction of 2/23/06. However, if applicant is willing to stipulate for the record that the inventions of Group I-III are ***obvious over each other***, the examiner would consider examining all the invention groups I-III together. Applicant's argument that there is no search burden has been considered and found not persuasive. The invention of group II is a product which is distinct from both a method of making and a method of using that could readily be used to make or use an unrelated product (such as tyrosinase), and therefore the methods would require non-coextensive searches. Thus a search and examination of any of the methods of groups I and III with each other or with the product of group II would be a search burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 7-8 are under examination.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying an agent that facilitates folding and exit of a normally cell surface-localized transmembrane domain-containing protein from the endoplasmic reticulum (ER), wherein said protein is tagged with a biotin target sequence in ***an extracellular domain***, does not reasonably provide enablement for a method for identifying an agent which corrects protein misfolding of a ***membrane-localized protein***, wherein said protein is tagged with a biotin target sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is an assay that relies on the ER-retention of the protein of interest, and the extracellular availability of the biotin tag should an agent overcome ER retention and allow surface trafficking of the protein. For the invention to work properly, the biotin tag must be available for modification with biotin by applied extracellular biotin synthase. The invention is complex because transmembrane proteins have both intracellular and extracellular aspects, which makes appropriate placement of the biotin-targeting domain complex. Further, the invention is recited as identifying agents for membrane-localized proteins. However, the invention only works for mutant forms of proteins normally localized to the plasma membrane which are retained in the ER by the ER quality control apparatus.

The prior art indicates that several mutant membrane proteins that get stuck in the ER have different transmembrane topologies. For instance, CFTR (See Chang et al., 1994) and Kv 1.1 (see Manganas et al, 2001). Placement of a biotin tag between transmembrane domains 6 and 7 (see Chang et al , for instance) will result in a tagged receptor that will not function appropriately in the assay (see page 18573, figure 1 of Chang et al) because the tag will not be available to extracellular biotin and biotin synthase. Furthermore, the proteins must be ***mutant forms that are retained in the ER*** of proteins normally trafficked to the plasma membrane. For example, Manganas et al (2001), Tamarappoo et al (1999) and Heda et al (2000) describe mutant forms of Kv 1.1, Aquaporin-2, and CFTR that are misfolded and remain retained in the ER by the ER quality control apparatus. In each case, a marker is used to ascertain what

conditions or agents may overcome the ER retention. For instance, Figure 6 (page 34829) of Tamarappoo et al. describes a change in glycosylation state (which indicates facilitated folding and surface trafficking) of Aquaporin-2 by administration of glycerol.

The breadth of the claims are such that they encompass tagged membrane proteins that would not function properly with the design of the assay. In particular, the assay would not be appropriate for membrane proteins ***normally*** localized to the Golgi, lysosomes, ER, endocytic vesicles, or other endosomes that reasonably do not result in extracellular, plasma membrane display of the target protein. Furthermore, the assay would not be appropriate for mutant proteins that do not result in ER retention.

Considering the nature of the invention, the state of the prior art, and the breadth of the claims, one skilled in the art would not be able to make or use the invention as currently claimed.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schatz (US patent number 5,874,239, filed July 28, 1994) and in further view of Heda et al (2000).

Schatz discloses biotin target sequences of the instant application for use in fusing generically to polypeptides for efficient biotinylation of the resulting fusion proteins (see abstract). Further, Shatz teaches exposing the tagged protein to biotin and adding exogenous biotin ligase (see summary of invention, col 3 and 4).

Schatz does not disclose biotinylation of cell surface proteins in an assay to identify reagents that facilitate folding of an ER retained membrane localized protein.

Heda et al discloses biotinylation of cell surface and total (as it relates to claim 8) CFTR in an assay to identify 'agents' (i.e., low temperature and sodium butyrate) that correct protein misfolding (and increase expression) of CFTR (see abstract). Heda et al. disclose obtaining a cell culture which expresses a misfolded membrane-localized protein, CFTR. Heda et al perform "surface biotinylation" (see page 660 under "surface biotinylation") by cross-linking biotin to all proteins containing glycosyl moieties (of which CFTR has several) after exposing the culture to low temperature or sodium butyrate, which act as agents that potentially correct misfolding of CFTR, wherein an increase in

biotin-labelled cftr indicated the agent worked (see Figure 2, band C). Note that the biotin-labelled CFTR is detected by the absence of band C in Figure 2a. Heda et al also report contacting the cell with a permeabilizing agent before detection (see page 660, left col, top paragraph).

In summary, Heda et al instructs as to how to use surface biotinylation in an assay designed to identify reagents that correct misfolded CFTR that remains stuck in the ER. Essentially, Heda et al instructs that if the agent does not work, there is no cell surface biotinylation of CFTR. Schatz simply discloses that a short biotin tag can be added to the target protein and will be biotinylated in the presence of biotin ligase. The only element that Heda et al does not teach is a specific biotin tag, biotinylated by biotin ligase rather than chemical cross-linking to glycosyl moieties presented on the cell surface.

One of ordinary skill in the art would have been motivated to combine the biotin tag of Schatz with the surface glycosyl moiety biotinylation of Heda et al because the tag of Schatz provides a more specific labeling of CFTR, and eliminates having to use a second, CFTR-specific antibody in the detection step (for instance in figure 2A).

## Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven Standley whose telephone number is **(571) 272-3432**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on **(571) 272-0867**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Steve Standley, Ph.D.
7/17/06

David S. Romeo
DAVID S. ROMEO
PRIMARY EXAMINER